



Sandhu, S., Piepho, H-P., & Khehra, H. S. (2017). Comparing the effectiveness profile of pharmacological interventions used for orthodontic pain relief: an arm-based multilevel network meta-analysis of longitudinal data. *European Journal of Orthodontics*, 39(6), 601-614. <https://doi.org/10.1093/ejo/cjw088>

Peer reviewed version

Link to published version (if available):
[10.1093/ejo/cjw088](https://doi.org/10.1093/ejo/cjw088)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Oxford University Press at <https://academic.oup.com/ejo/article/2997678/Comparing>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Comparing the effectiveness profile of pharmacological interventions used for orthodontic pain relief – An arm-based multilevel network meta-analysis of longitudinal data

Summary

Background and Objectives: To compare the effectiveness profile of various analgesics used for orthodontic pain relief over a one week time period by conducting a longitudinal network meta-analysis (NMA)

Search methods: The MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases were searched till 31st December 2015 to identify the relevant studies. Additional studies were identified by hand searching journals and reference lists. Unpublished literature was also searched.

Selection criteria: Eligible studies were randomised-controlled trials (RCTs) evaluating the effectiveness of pharmacological interventions for pain relief after placement of separator or initial aligning arch wire.

Data collection and analysis: Pain intensity data at 2 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, 96 hours, and 168 hours was collected. In addition, data was also extracted for potential covariates (age, sex and procedure). A covariate-adjusted arm-based multilevel random coefficient model was used for evidence synthesis.

Results: 15 RCTs (1,341 participants; male/females 595, 44.6% / 746 55.4%; mean age 17.3 years, SD 4.1) were included. A total of 11 Nodes (Acetaminophen, Aspirin, Etoricoxib, Flurbiprofen, Ibuprofen, Lumiracoxib, Meloxicam, Naproxen, Piroxicam, Placebo and Control) were identified out of which 5 Nodes (Placebo, Ibuprofen, Naproxen, Acetaminophen and Aspirin) had Subnodes (based on timing of administration). Compared to Control, Placebo, Flurbiprofen, Lumiracoxib and Meloxicam were not significantly effective. Etoricoxib (most effective) and Piroxicam (second most effective) were effective over a long period which lasted up to 96 hours and 72 hours, respectively. Ibuprofen, Acetaminophen, Naproxen and Aspirin were effective at 6 hours, 12 hours, and 24 hours. The effectiveness of these analgesics was significantly influenced by the timing of administration. Assessment of heterogeneity, transitivity, inconsistency, and publication bias revealed no major threat to the NMA derived estimates.

Conclusion: Compared to the Control, Placebo was least effective whereas Etoricoxib was most effective analgesic in reducing orthodontic pain. Administration timing has significant influence on the effectiveness profile of analgesics routinely used for managing orthodontic pain.

Registration: Not registered

Conflict of interest: None

Introduction

Various methods have been proposed to manage orthodontic pain which include pharmacological and non-pharmacological interventions. However, pharmacological interventions are more effective, and therefore, are most commonly used for orthodontic pain management (1). Recently, pairwise meta-analyses (PMAs) were conducted to evaluate the relative effectiveness of pharmacological interventions used for orthodontic pain relief after separators and/or initial arch wire placement (1, 2).

However, PMAs are limited in their Comparative Effectiveness Research (CER) based decision making value because such conventional meta-analysis approach does not utilize all the available evidence if direct comparisons are not provided by all studies included in the analysis (3, 4). Network meta-analysis (NMA) has extended this concept of CER by providing estimates for comparative effectiveness of all competing interventions even when no head-head comparisons are available (3, 4). Recently, Sandhu et al (5) conducted a NMA to examine the effectiveness of various intentions used for orthodontic pain relief. However, authors restricted their NMA to synthesize evidence for comparative effectiveness of various competing interventions for a single time point.

Recent advancements in NMA methodology within a framework of multilevel modelling allow appropriate handling of more complex data (such as correlated longitudinal data) in evidence synthesis; and to take into account the variability in treatment definitions (e.g. based on timing of administration) across network (6-9). Further, an arm-based NMA approach does not require a common comparator across the network (4).

In this review, an arm-based covariate adjusted multilevel NMA of repeated measure data was undertaken to address the specific research question which was defined within the PICOS (Population, Interventions, Comparator, Outcome, and Study type) framework.

Objective was to synthesize evidence based on the randomized clinical trials (RCTs) to compare the effectiveness profile of various competing pharmacological interventions against control for pain relief over a one week time for male and female participants undergoing orthodontic treatment after placement of orthodontic separator or initial arch wire. The selection of aforementioned time frame, i.e. one week, was based on the fact that it represents the clinically meaningful time period in terms of change in pain intensity level (10-12). We decided to include studies with orthodontic separator or initial arch wire because the patterns and magnitude of pain after placement of separator and initial arch are similar (10-13).

Methods

We followed a standard systematic review protocol according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines (14). However, this systematic review was not registered as *a priori*. Eligibility criteria and search strategy were designed to ensure that all possible pharmacological interventions used for orthodontic pain management are included in this NMA.

Eligibility criteria

Eligible studies were prospective randomised-controlled trials (RCTs) evaluating the effectiveness of pharmacological interventions over a one week time. To safeguard against violation of transitivity and consistency assumptions in NMA, we included studies with comparable design characteristics (objectives, methodology and outcome) and plausible range of covariate (e.g. age and sex) distribution (15). The target population was defined as the children and adults (both males and females) who required placement of orthodontic separator or initial arch wire as a part of their fixed orthodontic treatment.

Considering the fact that administration timing of pharmacological interventions varies (i.e. pre-operative, post-operative, and combination of pre-operative and post-operative) from

study to study, we decided to take into account this variability in treatment definition, as recommended (9). Please refer to Section A of Appendix 1 (Online Supplementary Material) for details.

The index for comparative effectiveness (outcome) amongst interventions was the difference in patient reported pain intensity level after separator or initial arch wire placement. Since we conducted an arm-based NMA, there was no need for studies to have a common comparator in all studies. This because in an arm-based NMA, it is assumed that each study hypothetically compares all interventions, many of which are missing by design and thus can be considered as missing at random (4). However, to compare an intervention effect against a single reference group, we used the ‘Control’ group as a comparator in our presentation of results of the NMA.

Search strategy

The MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), and EMBASE databases were searched to identify the randomized clinical trials (RCTs). These databases were searched till December 31, 2015 without any restriction for starting date of search, publication language or publication status (ahead of publication as online; or as print in the Journal). To eliminate the possibility of excluding any intervention from its inclusion in this NMA, we did not use interventions as search item, rather we searched all studies which had the keyword pain or discomfort in the title and/or abstract. All such retrieved studies were then searched to find whether these studies used any pharmacological intervention for orthodontic pain relief.

Additional studies were identified by hand searching of all volumes and issues of following four major orthodontic journals from 1980 to December, 2015: American Journal of Orthodontics and Dentofacial Orthopaedics, The Angle Orthodontist, the European Journal of

Orthodontics and the Journal of Orthodontics. Reference lists of the included studies and previously published systematic reviews/meta-analysis related to the topic were screened for identification of any additional study. Unpublished literature was searched in Pro-Quest Dissertations & Theses database, ClinicalTrials.gov, and National Research Register using “orthodontic” and “pain” as search terms. Conference proceedings and abstracts were also accessed where possible.

Study selection and data extraction

The titles and abstracts of all studies identified by the search strategies were independently screened by the first author (S.S.S) for removal of duplicate entries and studies which failed to meet the objectives of this NMA. Full-text articles of remaining studies were assessed independently by two authors (S.S.S and H.S.K) for eligibility based on the predefined criteria. When disagreement occurred, the article was re-read and discussed until a consensus was obtained amongst the authors. A record of all decisions made about the identified studies was kept. The review authors were not blinded to author(s), institution or site of publication of studies.

Study characteristics data was extracted independently by two review authors (S.S.S and H.S.K) using a pilot tested data extraction form. We resolved disagreement by mutual discussion and, if required, by consultation with a third author. The data extracted was: 1) study identification: first author’s name and year of publication, 2) study design, 3) population (participants): sample size, mean age, number of male and female participants, and female proportion, 4) interventions: details of pharmacological interventions including the dose, frequency, mode and timing of administration, 5) comparator, and 6) outcome assessment.

Details of data extracted, and the methodology used to extract the required data is presented in the Section B of Appendix 1 (Online Supplementary Material). Briefly, the

predefined primary outcome of interest was the patient reported pain intensity level over a one week time. We included trials which assessed pain intensity by using a 100 mm Visual Analogue Scale (VAS) or a 10 cm VAS scale. We extracted data for each time point as reported in each individual study. The earliest time point for outcome assessment reported across studies was 0 hours (baseline), i.e., before randomization. The farthest time point for outcome assessment was 168 hours (day 7) after separator or initial arch wire placement. The total number of time points identified across all studies for outcome assessment was 10; time points were defined as 0 hours (baseline), 2 hours, 6 hours, 12 hours, 24 hours (day 1), 36 hours (day 1 night), 48 hours (day 2), 72 hours (day 3), 96 hours (day 4), and 168 hours (day 7). If a trial reported multiple effect sizes (e.g. at rest, during fitting teeth together etc.), we combined these effect sizes to get a single estimate, as recommended (14). We followed a recommended procedure to extract relevant data from non-parallel (split-mouth and cross-over) design RCT in order to include it in the meta-analysis along with the rest of the parallel design RCTs (14). Based on the evidence available on the potential confounders influencing the outcome in pain trials, we extracted data for five potential confounders which were to be included as *a priori* covariates in our NMA. Out of these five potential covariates, three were patient level (age, sex and baseline pain) covariates (16-18), and two were study level covariates (the double blinding procedure (19) and the orthodontic procedure (10, 11)).

Risk of bias assessment for studies included trials

Risk of bias was assessed independently by two authors (S.S.S and H.S.K) and all disagreements were resolved by discussions. The Cochrane Collaboration risk-of-bias tool (14) was used to assess the risk of bias based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting of outcomes and ‘others’ sources of bias. The ‘others’ source of bias was based on the assessment whether male and female

participants were similar with respect to the mean age. This ‘others’ source of bias was used to assess the transitivity assumption. Risk of bias assessment was based on the reported information and no attempt was made to contact the authors for clarification. If information was not sufficient to ascertain the level of bias (High vs Low), we assigned the level ‘Unclear’ for risk of bias.

Statistical analysis

Data was analysed with SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Mixed model analysis (PROC GLIMMIX) was employed to analyse repeated measures data (VAS score) appropriately accounting for the correlated nature of the data (20) and assuming normality of the response. The statistical significance level was set at 0.05. The effect size (mean difference) was considered significant if a 95% Confidence Interval (CI) did not include ‘zero’. The Stata software (21) version 14 (StataCorp, College Station, Tex) was used for ranking interventions based on a multidimensional scaling (MDS) approach (22). The required pairwise estimates were derived from the mixed model analysis (PROC GLIMMIX). For plotting the network evidence, we used the ‘igraph’ package (version 1.0.1) in R (version 3.2.4) software. Time was modelled as continuous variable. The unit of time in this NMA was hour, ranging from 2 hours to 168 hours (day 7). It was decided that baseline pain, i.e., pain assessment before randomization (time ‘0’ hours), would be used as a covariate.

Details of methodological background, the analytical strategies including modelling of the time variable, description of various models explored for current NMA, and model fitting and its evaluation are described in the Section A, Section B and Section C of Appendix 1 respectively (Online Supplementary Material). Briefly, a recently developed arm-based multilevel (mixed effect) modelling approach within a framework of two-way factorial analysis-of-variance (ANOVA) was used (7). The data constituted a hierarchical structure with repeated measure outcome nested in Subnodes which in turn were nested in Nodes. An inverse

variance weighed quadratic random coefficient model was fitted using the restricted maximum likelihood (method=RMPL) method of estimation and Kenward-Roger degree of freedom (20).

Age, sex (proportion of females) and procedure (separator or initial arch wire) were entered into the model as a part of network meta-regression (15). These covariates were included to adjust the parameters estimates for the potential confounding effect on the outcome (i.e. pain). The reasons for excluding other covariates are provided in the Appendix 1 (Online Supplementary Material).

Testing assumptions of transitivity, consistency, heterogeneity and publication bias

Details are provided in the Section D of Appendix I (Online Supplementary Material). The plausibility of transitivity assumption was evaluated based on the design characteristics and the methodology of studies included in the NMA, as recommended (23). We adopted and extended the design-by-treatment interaction approach recently used by Piepho et al (6) for evaluation of heterogeneity and inconsistency across a network in arm-based NMA. To assess publication bias, i.e., small study effects (effect size with large standard error, SE), we adopted a similar approach as was used in a recent NMA (8). In this approach, a study-level explanatory variable representing a measure of precision (Standard Error) was added to test if the intervention effect varies with the study precision.

Although it is a routine practice to conduct a conventional pairwise meta-analysis (PMA) as part of evidence synthesis in order to assess the agreement/disagreement between the direct estimates derived from the PMA and NMA, (23) we realized that it was not feasible and informative in this current review. This was because of the complexity of model and limited data available to derive a meaningful interpretation of PMA findings. Please refer to Section E of Appendix 1 (Online Supplementary Material) for more details.

Results

Search results and characteristics of studies included in the NMA

The search strategy details are provided in the Appendix 2 (Online Supplementary Material). A total of 256 RCTs were identified by the search strategy. After removing duplicate records (108) and studies such systematic reviews and trials which either did not use orthodontic separator/initial arch wire as part of orthodontic procedure or did not assess pain as outcome etc. (101), we were left with a total of 47 RCTs for which full text articles were obtained to select relevant RCTs to be included in this review. After scrutinizing the full text articles, for the predefined eligibility criteria, in total 15 RCTs (24-38) were included in this review. The PRISMA flow diagram is shown as Figure 1. Further details are provided in the Section F of Appendix 1 (Online Supplementary Material).

The characteristics of studies included in the NMA are presented in the Appendix 3 (Online Supplementary Material) and summarised in Table 1. Total 1,341 participants (595 male, 44.6%; females=746, 55.4%) were included with mean age of 17.3 years (SD 4.1), and mean baseline pain VAS score 2.54 (SD 0.6). Eleven RCTs (73.3 %) used orthodontic separator as orthodontic procedure (24-27, 29-32, 36-38) whereas the remaining 4 RCTs (26.7 %) used initial arch wire as orthodontic procedure (28, 33-35). Except one RCT (26), all trials were single centre trials.

Two RCTs were two-arm trial (25, 26), 10 RCTs were three-arm trials (24, 27-31, 33, 35, 36, 38), two RCTs were four-arm trials (32, 37) and one RCT was a six-arm trial (34). Except one RCT (32), which was a cross-over trial, all remaining 14 RCTs were from parallel arm designs. Since there was no evidence of carry-over effects, the cross-over design RCT, which compared four interventions, qualified for inclusion as a four-arm trial in the NMA along with other parallel design trials (as explained in the methodology section).

VAS was used for outcome (pain) assessment across all studies. The time of outcome assessment varied from 2 hrs to 168 hrs (day 7). Two RCTs (13.3 %) recorded baseline assessment of pain before randomization and analgesics administration (25, 35). The number of studies contributing to data at each time point was as follows (with number of studies in parentheses): baseline (2), 2 hours (15), 6 hours (15), 12 hours (11), 24 hours (15), 36 hours (2), 48 hours (12), 72 hours (9), 96 hours (3), and 168 hours (9).

Description of Network

The evidence network plots are shown in Figure 2. In all, 11 Nodes (Acetaminophen, Aspirin, Etoricoxib, Flurbiprofen, Ibuprofen, Lumiracoxib, Meloxicam, Naproxen, Piroxicam, Placebo and Control) were identified, out of which 5 Nodes (Placebo, Ibuprofen, Naproxen, Acetaminophen and Aspirin) had Subnodes (based on timing of administration). Placebo, Ibuprofen and Acetaminophen had three Subnodes whereas Naproxen and Aspirin had two Subnodes. The details are provided in Table 1.

Risk of bias assessment

Risk of bias assessed for each individual study is shown in Figure 3. There was no evidence for high risk of bias for randomization and allocation procedures, though few studies did not provide relevant information and thus were assigned the level 'unclear risk of bias'. Since we were investigating the efficacy of pharmacological interventions, the focus for evaluation of risk of bias related to the blinding was based on the 'double blinding' procedure. Therefore, based on the consensus amongst authors, a high risk of bias was assigned to a study if it failed to meet the criteria for double blinding. We identified one study (30) with high risk of bias for blinding.

Model fit evolution and testing assumptions of transitivity, consistency, heterogeneity and publication bias

The best fitting model identified was one with random intercept and slope (random coefficients) at study level as well as at the level of nested random structure (Study/Node/Subnode). All models described are covariate adjusted unless otherwise stated. Please see Section C of Appendix 1 (Online Supplementary Material) for more details. Results for multilevel model assumption evaluation (e.g. normality, autocorrelation of residuals etc.) and model fit assessment are shown in Appendices 4 and 5 (Online Supplementary Material).

A careful evaluation of methodology and other characteristics of studies (Appendix 3 of Online Supplementary Material) included in this NMA revealed no potential threat to the transitivity assumption. Results for joint global test for inconsistency and heterogeneity showed no evidence of significant inconsistency or heterogeneity at Node or Subnode level. Due to the sparsity of data in terms of number of studies per design, as shown in Table S1 of Appendix 1 (Online Supplementary Material), we could not investigate the design specific-contribution to overall heterogeneity (study-by-design-by-intervention interaction) across the network.

Findings of meta-regression based approach used to assess publication bias (small study effect) revealed no significant publication bias at Node level. However, there was an evidence for significant publication bias for Subnodes corresponding to two Nodes, namely, Ibuprofen and Placebo. Compared to Pre-operative Ibuprofen, the small study effect significantly enhanced the (apparent) effectiveness (i.e. slow rise in pain) of Ibuprofen administered as combined Pre-operative and Post-operative analgesia and also resulted in significantly faster deceleration in the rise in pain. On the contrary, compared to Pre-operative Placebo, the small study effect significantly decreased the effectiveness of Placebo administered as combined Pre-operative and Post-operative analgesia as well as resulted in significantly slower deceleration in the rise of pain. Readers are referred to Section G of Appendix 1 (Online Supplementary Material) for more details about findings of transitivity, consistency, heterogeneity and publication bias assessment.

Network meta-analysis results

Results for covariate adjusted and non-adjusted quadratic random effect network meta-analysis are shown in Table S3 and Table S4, respectively of Appendix 1 (Online Supplementary Material). Since model fit was substantially better for the covariate adjusted model, we will be presenting results derived from the covariate adjusted network meta-analysis. Detailed interpretation of regression estimates derived from the covariate adjusted NMA (Table S3) model are provided in the Section H of Appendix 1 (Online Supplementary Material).

Our model allows estimation of interventions' effectiveness (Node) as well as the effect of administration timing (Subnode) on the effectiveness profile and since it is more meaningful to have a clear understanding of effectiveness profile at each time point compared to the Control group, we will be presenting these results in the following sections. Reader are referred to Section H of Appendix 1 (Online Supplementary Material) for more detailed description of findings.

Node Effectives at each time point (compared to Control group)

The forest plots showing the comparative effectiveness (estimate as well as the corresponding 95% Confidence Intervals) of each Node are displayed as Figure 4 through Figure 12. An estimate was considered significant if the corresponding 95% CI did not include zero. It is worth noting that estimates are more precise for Nodes (Placebo, Ibuprofen, Naproxen, Acetaminophen and Aspirin) which have nested Subnodes. More detailed results (regression curves and profile plots) are provided in the Appendix 6 (Online Supplementary Material).

Etoricoxib was most effective intervention throughout a one week time period with its effectiveness reaching a peak at around 12 to 24 hours. Except for 168 hours (day 7), Etoricoxib

was significantly effective in reducing pain when compared to the Control group. Piroxicam was significantly effective at 2 hours, 12 hours, 24 hours, 36 hours, 48 hours and 72 hours; whereas Naproxen was significantly effective at 2 hours, 6 hours, 12 hours, 24 hours, and 36 hours. The effectiveness profile of Ibuprofen, Aspirin and Acetaminophen was similar as these three interventions were effective at 6 hours, 12 hours and 24 hours. Placebo, Flurbiprofen, Lumiracoxib and Meloxicam were not significantly effective compared to the Control group at any of the time points included in this longitudinal NMA.

The pairwise differences for Nodes are provided in the Appendix 7 of Online Supplementary Material. The ranking of Nodes (compared to Control group) derived from these pairwise differences based on the Unique Dimension approach is provided in Table 2 and displayed as graph in Appendix 8 of Online Supplementary Material. Over the entire one week time period, Etoricoxib was most effective intervention (rank 1) whereas Placebo (rank 10) was the least effective intervention.

Subnode Effectives at each time point (compared to Control group)

Except for Placebo, the differences in the administration timing of all other four Nodes (with Subnodes) had significant influence on the effectiveness profile over time. The regression curves, forest plots as well as the profile plots are shown in the Appendix 9 of the Online Supplementary Material.

Acetaminophen, Aspirin, Ibuprofen and Naproxen administered as combination of pre-operative and post-operative analgesia were more effective as compared to administration of either pre-operative or post-operative analgesia. Pre-operative Acetaminophen was significantly effective only at 6 hours whereas the combination of pre-operative and postoperative Acetaminophen was significantly effective at 6 hours, 12 hours, 24 hours, 36 hours, and 48 hours. Aspirin administered as post-operative was not effective at any of the time

points but when administered as combined pre-operative and post-operative analgesia, it was significantly effective at 2 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, and 72 hours. Administration of Ibuprofen as combination of pre-operative and post-operative analgesia was significantly effective at 2 hours, 6 hours, 12 hours, 24 hours, 36 hours, and 48 hours whereas when administered as either pre-operative or post-operative, it was not significantly effective. Naproxen administered as pre-operative analgesia was significantly effective only at 2 hours whereas its administration as combined pre-operative and post-operative analgesia was significantly effective at 6 hours, 12 hours, 24 hours, 36, and 48 hours.

The pairwise differences for Subnodes are provided in Appendix 10 of Online Supplementary Material. The ranking of Subnodes estimated from the pairwise differences based on the Unique Dimension approach is provided in Table 3 and displayed as graph in Appendix 11 of Online Supplementary Material.

Considering the large number of possible pairwise comparisons for Nodes and Subnodes across nine different time point in this NMA, we did not undertake the Grading of Recommendations Assessment, Development (GRADE) assessment. One option was to perform GRADE assessment for overall estimates but this did not seem appropriate because our findings and interpretations were based on the interventions' effectiveness at individual time points.

Discussion

In general, our results substantiate various claims made recently in relation to the NMA. First, multilevel analysis of hierarchical data structure does provide precise estimates even when number of interventions is large and few studies are available for each comparison (5, 8, 9). This gain in precision was more pronounced for Nodes which had at least two Subnodes. Second, categorizing interventions (Subnodes) into their respective Nodes based on their

timing of administration did provide a valuable insight into the relative effectiveness of each intervention as a function of administration timing. This finding is in complete concurrence with the evidence provided by Giovane et al. (9) who concluded that network meta-analysis models should appropriately account for the variability in the intervention definitions in order to draw a meaningful interpretation of relative effectiveness.

Results show that compared to the Control group, Placebo, Flurbiprofen, Lumiracoxib and Meloxicam were not significantly effective in reducing pain at any of the time points included in this longitudinal NMA. Placebo was least effective and this finding is in agreement with the results of a recent meta-analysis (39) as well as a network meta-analysis (5) wherein the authors concluded that placebo response is significant only at the earliest time period within few minutes (39) and there is no evidence of significant placebo response at longer time periods (5, 39).

Etoricoxib, administered as combined pre-operative and post-operative analgesia, was the most effective intervention. This finding is in agreement with previous studies which reported that etoricoxib is more effective in reducing the acute pain, including orthodontic pain (5) as compared to other commonly used NSAIDs (40). Etoricoxib is a second-generation, highly selective cyclooxygenase 2 (COX-2) inhibitor with anti-inflammatory and analgesic properties (41). It has a dose-dependent inhibitory effect on COX-2 across the therapeutic dose range and possesses a long plasma half-life duration of 22 h (41). The high effectiveness of Etoricoxib observed in our NMA could be attributed to the fact that due to its administration as combined pre-operative and post-operative analgesia, there was an accumulative dose of 120 mg (60 mg pre-operative and 60 mg post-operative) administered within few hours (as evident from the study characteristics shown in Appendix 3 of Online Supplementary Material), thereby enhancing its effectiveness which is a dose-dependent phenomenon.

Our findings provided interesting insights into the pharmacokinetics-driven effectiveness of various analgesics used for managing orthodontic pain. Results show that the effectiveness of analgesics depends on the pharmacokinetics, and, therefore, should be carefully considered during the selection of analgesics in terms of administration timings. For example, analgesics with long plasma half-life, like Piroxicam (18-20 h), Naproxen (approximately 15 h) and Lumiracoxib (12 h) were effective over the longer time period even when administered as only pre-operative analgesic (41). On the contrary, the analgesics with shorter plasma half-life like Ibuprofen (4-8 h), Acetaminophen (2-5 h) and Aspirin (approximately 6 h) were effective over a longer time period only if these analgesics were administered as combination of pre-operative and post-operative analgesics (41).

We are aware of only one NMA reported in the orthodontic literature which provided the comparative effectiveness of interventions used for orthodontic pain relief (5). However, unlike our NMA which was based on a longitudinal data, previous NMA (5) included only a single time point (24 hours) for evidence synthesis. Therefore, we believe that the current NMA is an important advancement in the direction to evaluate the effectiveness profile of analgesics, particularly in assessing the effect of administration timing on the effectiveness over a one week time period. In general, our findings support the evidence provided by other authors (5) that placebo is least effective whereas Etoricoxib is most effective in managing orthodontic pain over a one week time period, including a peak pain intensity level at 24 hours.

Implications for practice and research

Findings of this NMA suggest that prescription of pharmacological interventions (analgesics) should be guided by an appropriate knowledge of their mechanism of action as well as the pharmacokinetics such as plasma half-life period. Based on such knowledge, a clinician may build his/her own analgesic protocol using the multimodal analgesia. An

important component of multimodal analgesic therapy is the pre-operative analgesia followed by adjuncts analgesics in form of post-operative analgesics. Pre-operative analgesia is an anticipatory anaesthetic approach that intends to prevent the pain and inflammatory response initiated by surgical incision and manipulation, and prevent the "wind-up phenomenon" (41). We also believe that our NMA would help in guiding the design of future trials in orthodontic pain management. This would fill the existing gap wherein no evidence is available for the possible effect of administration timing on the effectiveness profile of few analgesics used for managing orthodontic pain.

However, we would like to highlight the fact that since we synthesized evidence for the comparative effectiveness based on only therapeutic efficacy, and not on combined therapeutic efficacy and adverse effects (because studies did not report adverse effects), the above statements are generalized in nature and not specific.

Strengths and limitations

The strengths of this NMA include: a) we were able to extract the required data from all 15 relevant RCTs identified by a comprehensive search strategy, thus minimizing the selection and reporting bias; b) the novel multilevel analysis approach used to perform NMA imparts confidence in our results because such an approach can handle a complex network of evidence with sparse data (even does not require a common controls to be present in all trials), and yet provide precise estimates owing to the borrowing of strength across; c) lastly, the current model allowed us to have independent estimates and rankings of each individual Node as well as Subnode.

However, there are many limitations: a) Perhaps the most important limitation relates to the fact that few interventions (Nodes) included in this NMA did not provide data for the corresponding Subnode because of their single administration timing (pre-operative or post-

operative analgesia only). Thus, the precision of estimates varied across Nodes and few estimates had wide confidence intervals. However, the analytical methodology adopted in this NMA minimized such variability; b) there was an evidence for significant publication bias at Subnode level. However, this bias was confined to only two Subnodes (Ibuprofen and Placebo), and therefore we believe that it did not substantially affect the NMA estimates across the network; c) due to the limited number of studies available in each design, we were unable to quantify and locate the design specific heterogeneity and inconsistency across network. However, a joint global test for heterogeneity and inconsistency showed that there was no significant threat to the NMA estimates; and d) lastly, because of limited number of studies and relatively large number of interventions included in this NMA, we were unable to conduct few sensitivity analysis such as: i) to evaluate effect of network geometry on the NMA, ii) to examine impact of Nodes associated with publication bias on estimates by eliminating these Nodes from the network, and iii) to see if risk of bias had any influence on the estimate and ranking of intervention. An attempt to undertake first two sensitivity analysis could have resulted in an unconnected network structure, therefore was not feasible; whereas third sensitivity analysis deemed inappropriate, as explained next. An appropriate strategy to examine the effect of risk of bias for any domain, say for example double blinding, was to include a dummy covariate (e.g. 0, low risk; 1, high risk) within the framework of network meta-regression. However, since only one study had high risk of bias for double blinding (and rest all with low risk of bias), the results could have been misleading due to the ecological bias, a phenomenon well known for meta-regression. Similar implications were for other domains of risk of bias.

Conclusions

Results show that placebo response is not effective in managing orthodontic pain at any time point after orthodontic separator or initial arch wire placement. Etoricoxib seems to be

most effective analgesic over the entire one week duration after administration owing to its dose-dependent analgesic effectiveness and long plasma half-life period. Timing of administration has significant influence on the effectiveness profile of analgesics due to the inherent variability in the plasma half-life of various analgesics used for orthodontic pain management.

Figure captions

Figure 1 PRISMA flow diagram.

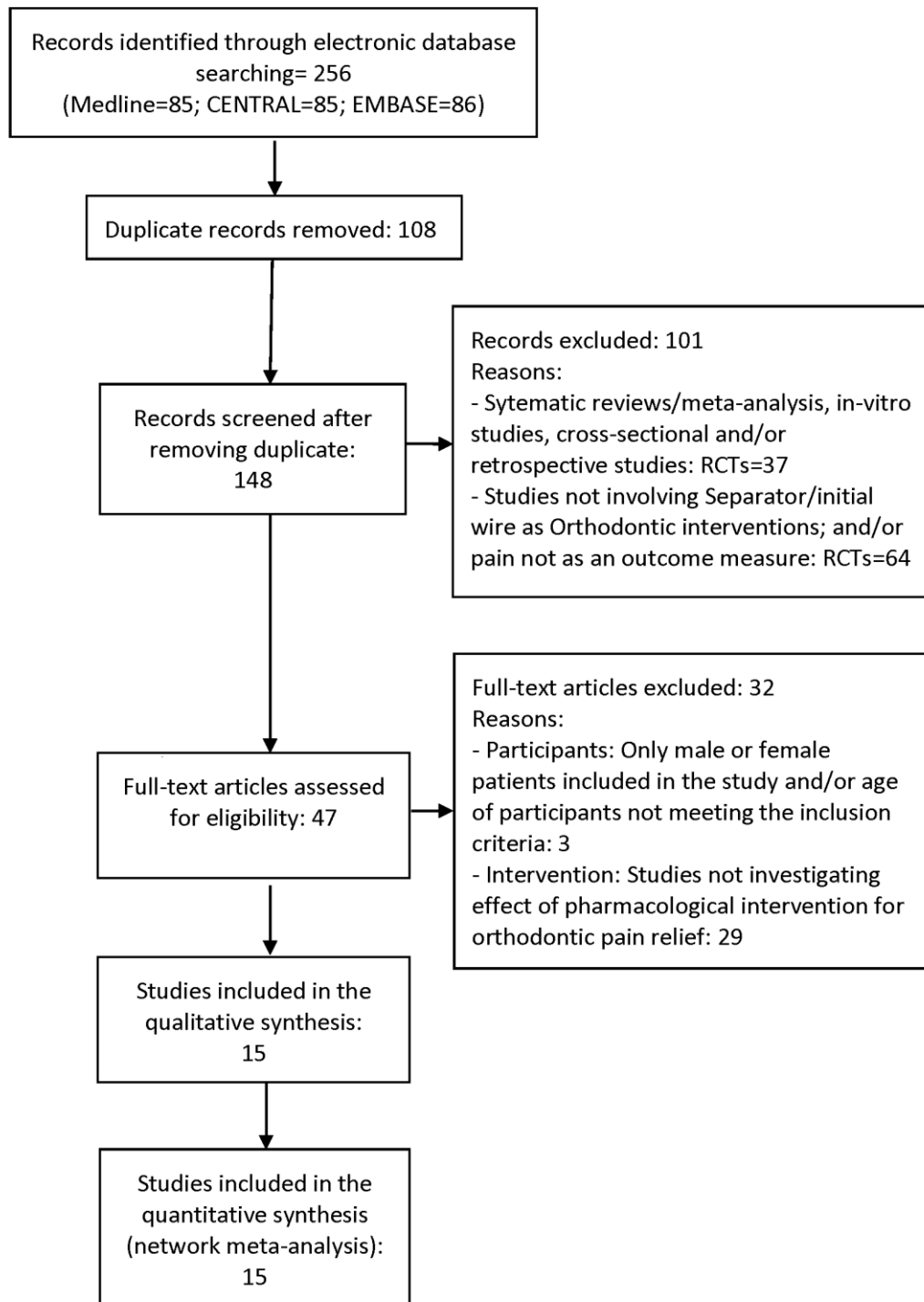
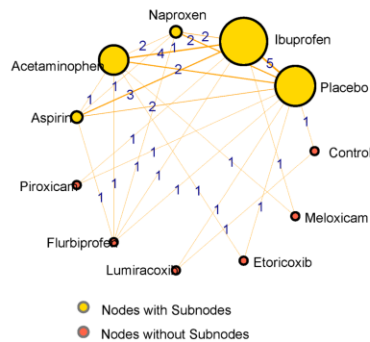
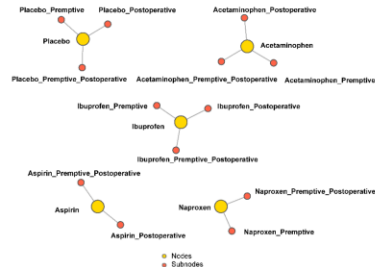


Figure 2 Network evidence plots at Node and Subnode level. Thickness of Nodes/Subnodes correspond to the total number of studies. The edge thickness (with numbers) shows the total number of studies making a direct comparison.



Network Evidence Plot (Subnodes constituting Nodes)



Network Evidence Plot (Subnode level)

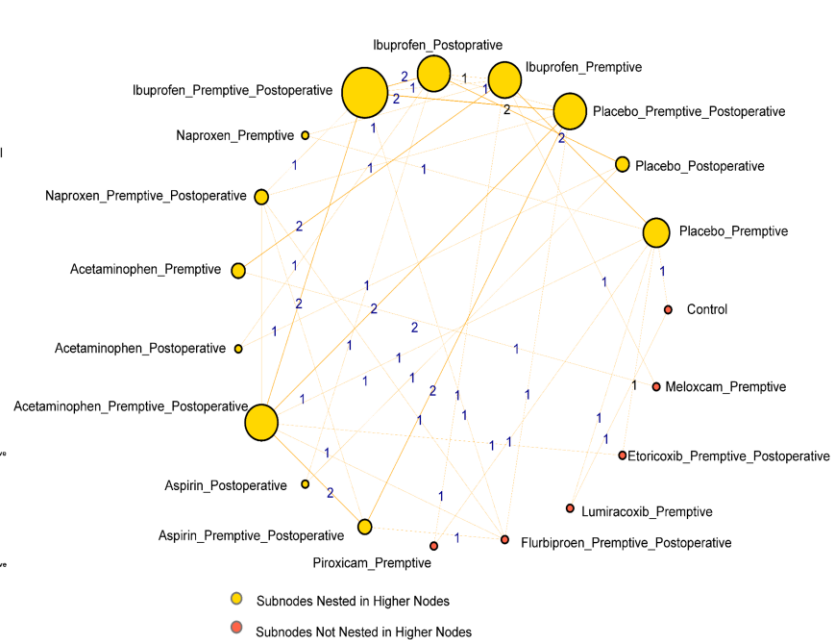


Figure 3 Risk of bias summary.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bernhardt et al, 2001	?	?	+	+	+	+	+
Bird et al, 2007	+	+	+	?	+	+	+
Bradley et al, 2007	+	+	+	?	+	+	+
Bruno et al, 2011	+	?	+	+	+	+	+
Gupta et al, 2014	+	+	+	+	+	+	+
Kohli et al, 2011	?	?	+	?	+	+	+
Minor et al, 2009	?	?	-	-	+	+	+
Ngan et al, 1994	?	?	+	?	-	+	+
Nobrega et al, 2013	+	+	+	+	+	+	+
Patel et al, 2011	?	?	+	-	+	+	+
Polat and Karaman, 2005	?	?	+	-	+	+	+
Polat et al, 2005	?	?	+	-	+	+	+
Salmassian et al, 2009	?	?	+	?	?	+	+
Steen Law et al, 2000	?	?	+	?	+	+	+
Sudhakar et al, 2014	?	?	+	+	+	+	+
Zarif et al, 2015	+	+	+	+	+	+	+

Figure 4 Forest plot showing Nodes effectiveness at 2 hours (compared to control group).

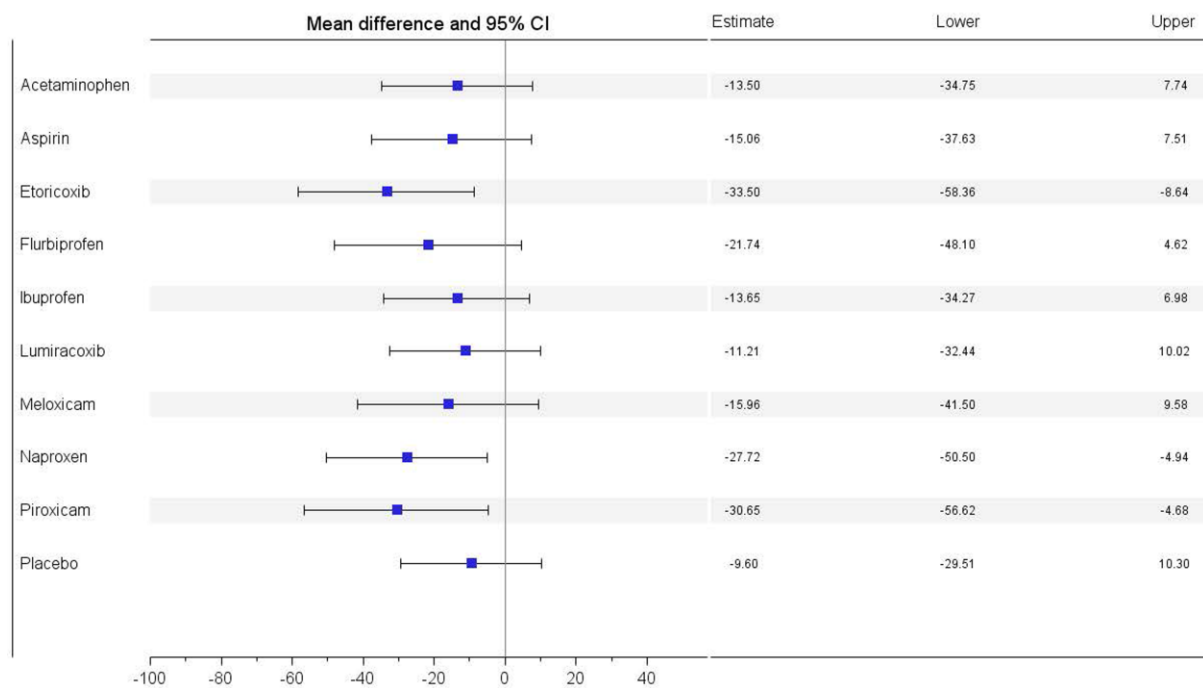


Figure 5 Forest plot showing Nodes effectiveness at 6 hours (compared to control group).

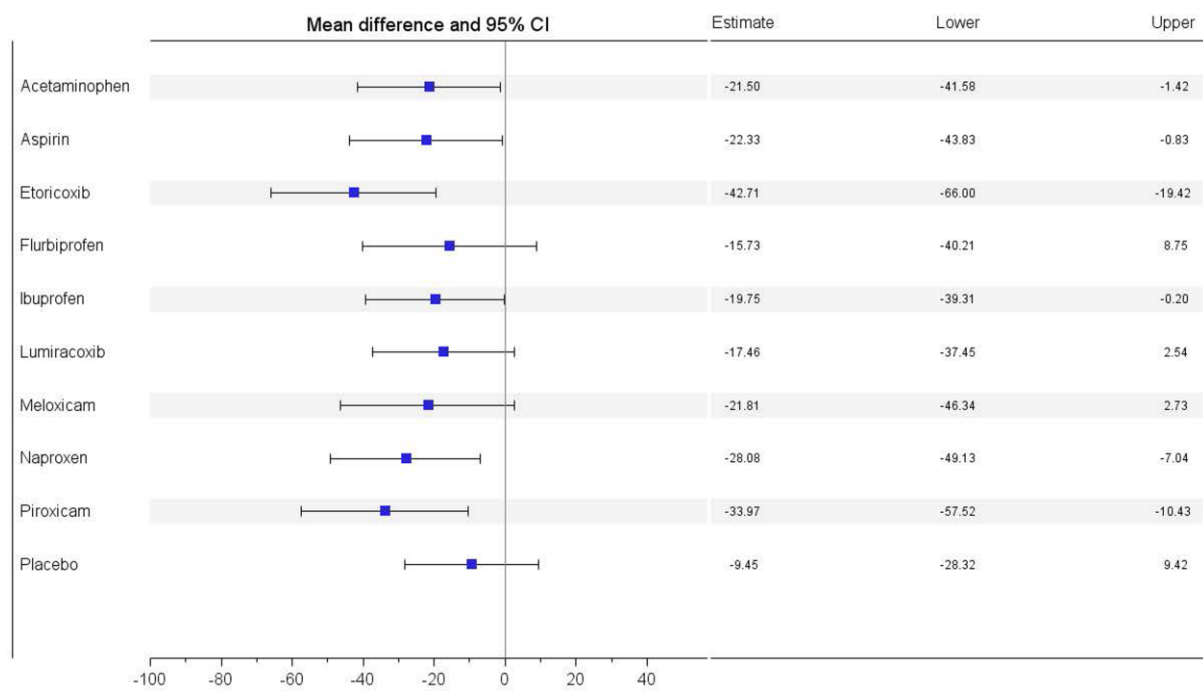


Figure 6 Forest plot showing Nodes effectiveness at 12 hours (compared to control group).

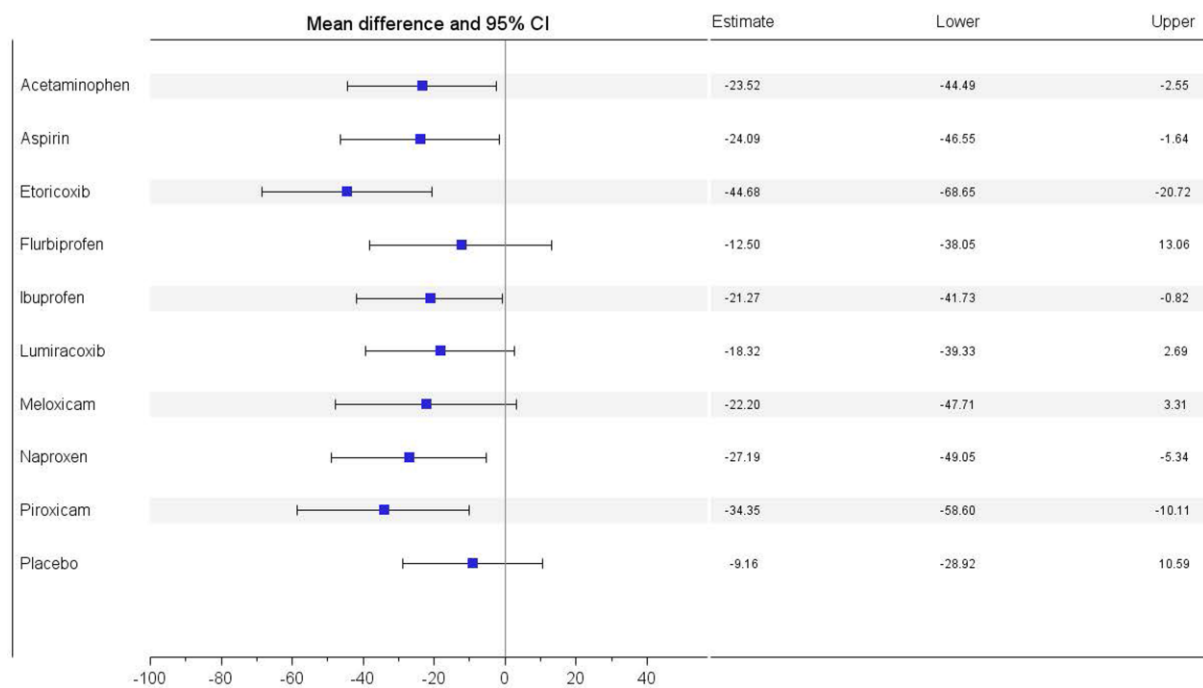


Figure 7 Forest plot showing Nodes effectiveness at 24 hours (compared to control group).

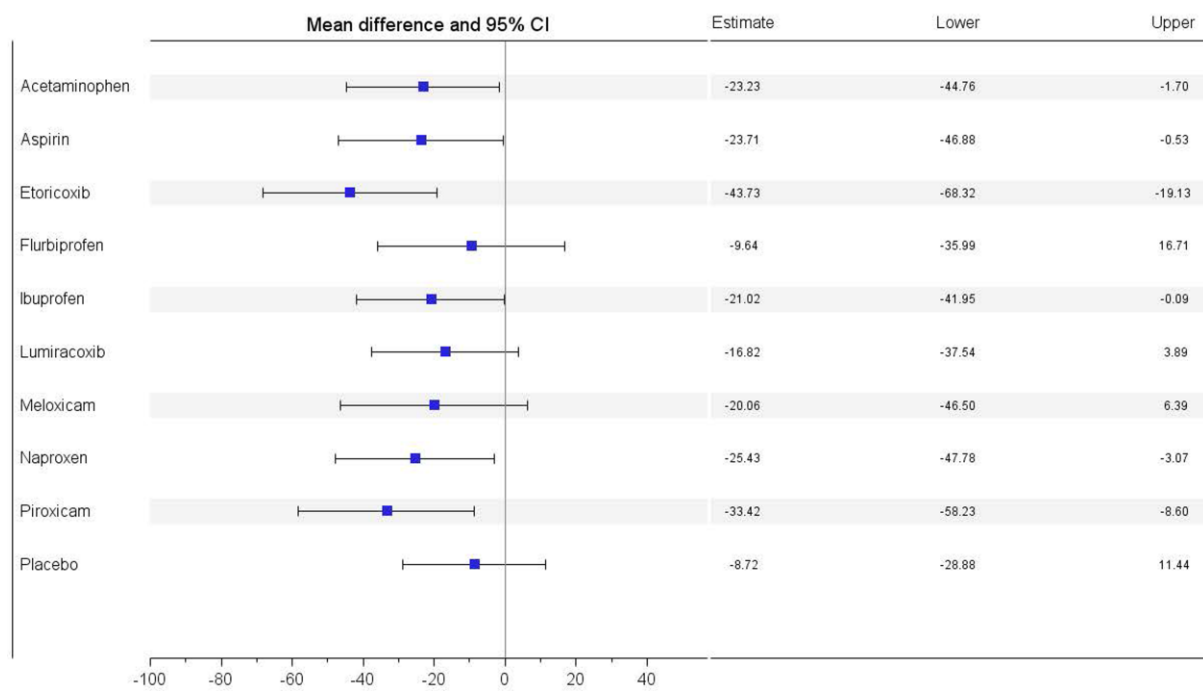


Figure 8 Forest plot showing Nodes effectiveness at 36 hours (compared to control group).

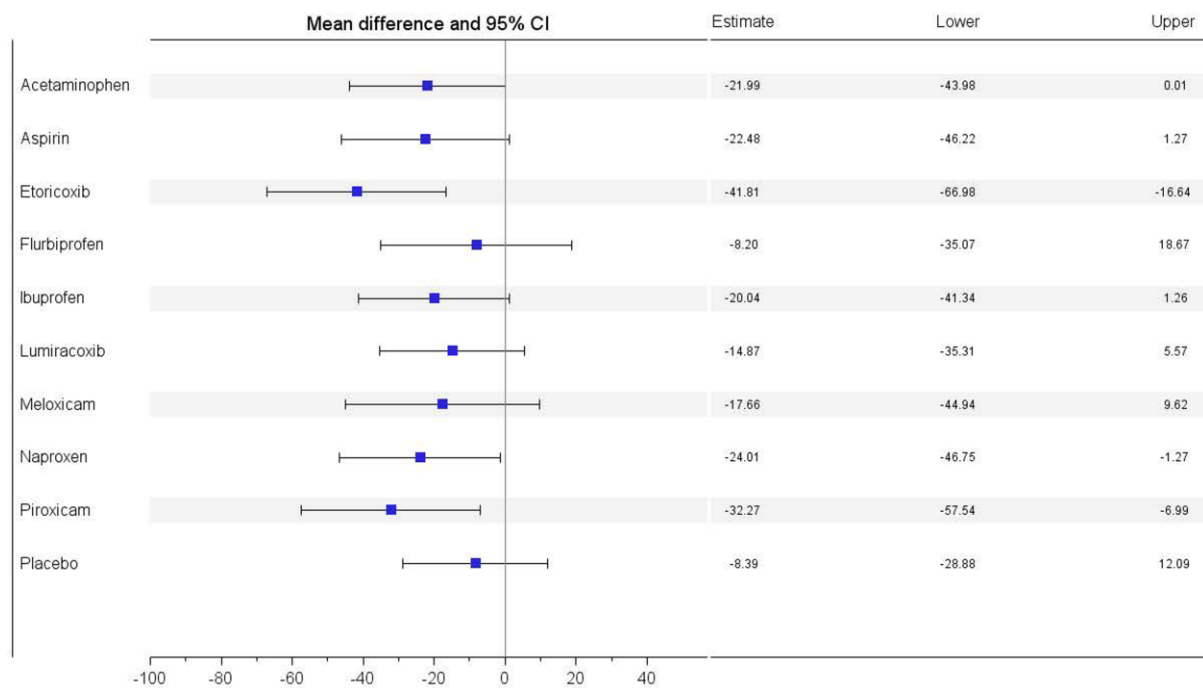


Figure 9 Forest plot showing Nodes effectiveness at 48 hours (compared to control group).

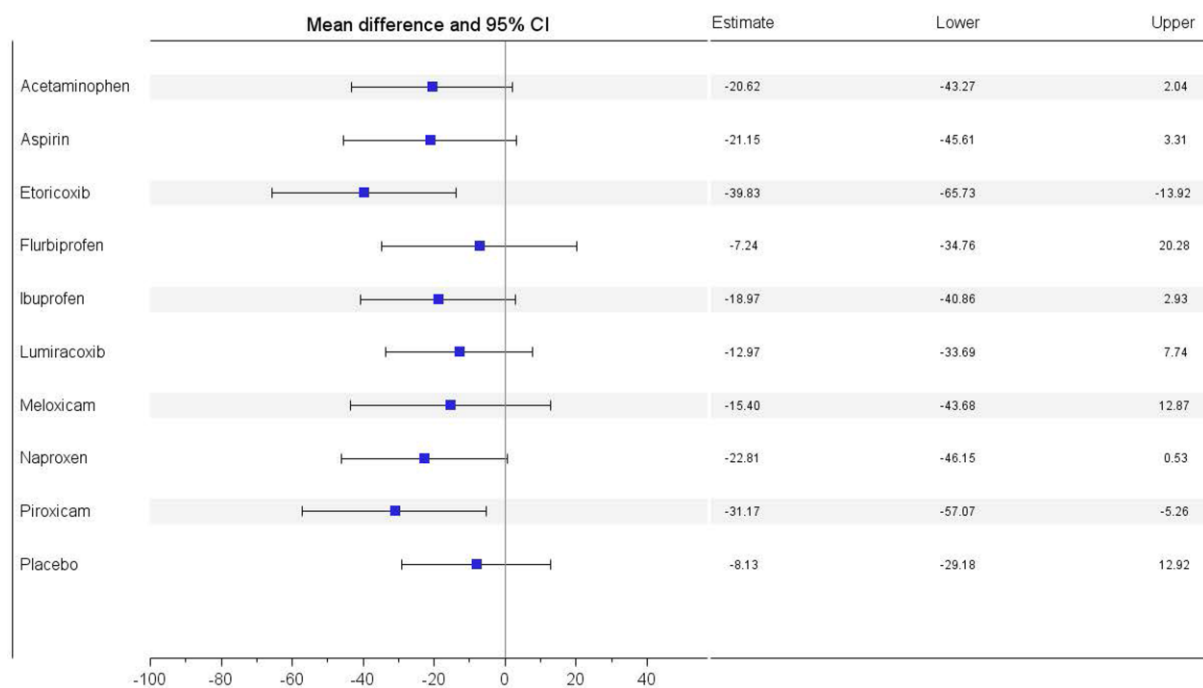


Figure 10 Forest plot showing Nodes effectiveness at 72 hours (compared to control group).

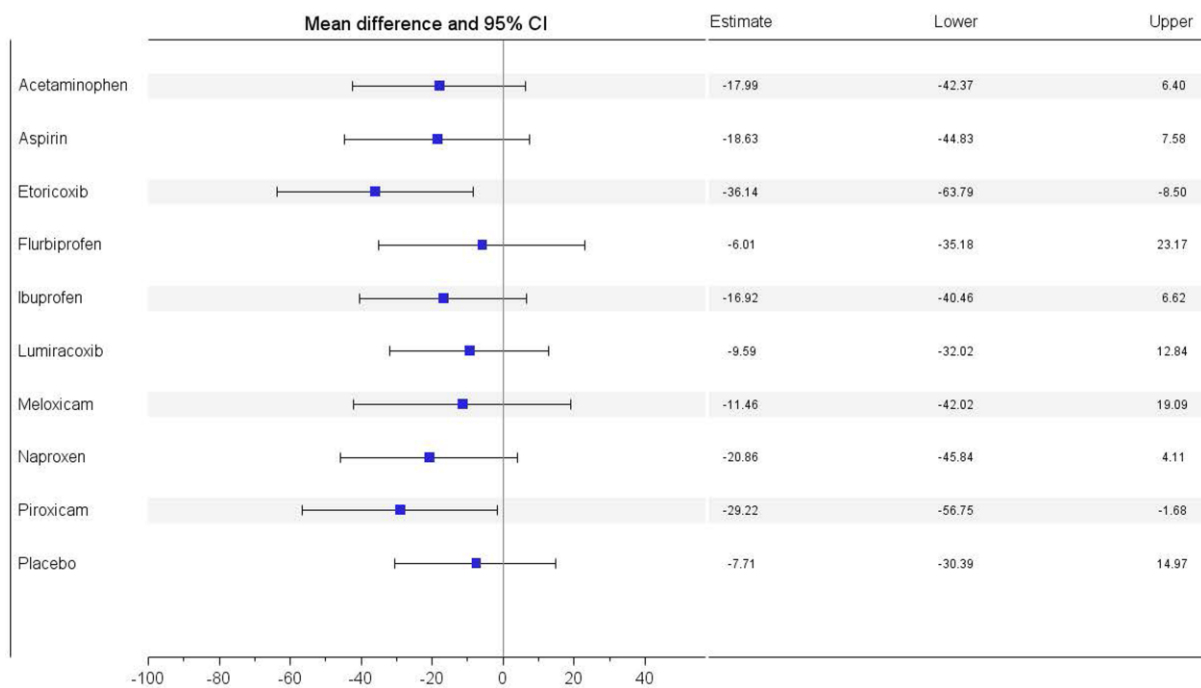


Figure 11 Forest plot showing Nodes effectiveness at 96 hours (compared to control group).

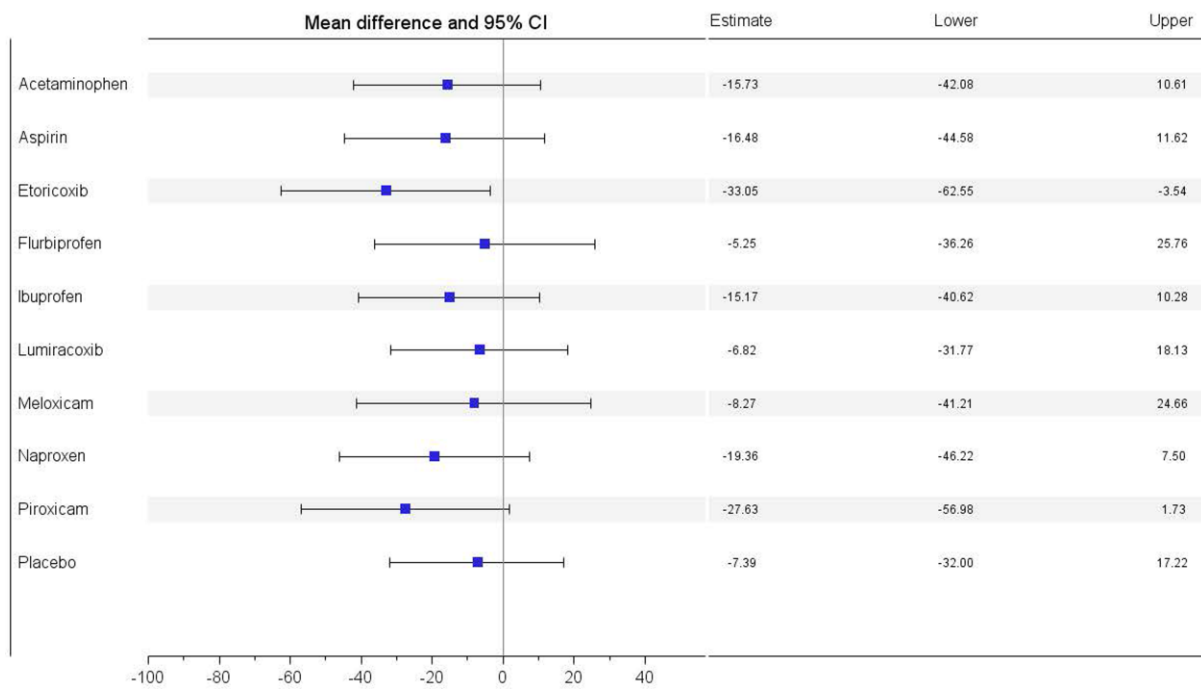
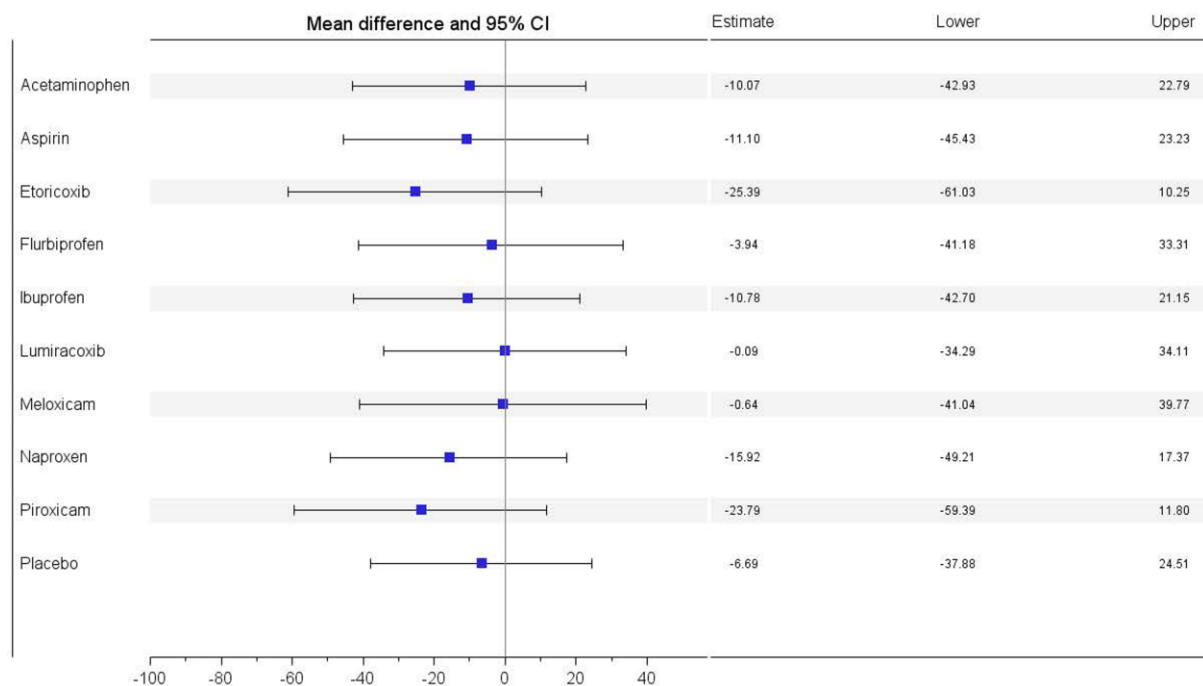


Figure 12 Forest plot showing Nodes effectiveness at 168 hours (compared to control group).



Conflict of Interests

Authors declared no conflicts of interest

References

1. Xiaoting, L., Yin, T., and Yangxi, C. (2010). Interventions for pain during fixed orthodontic appliance therapy. A systematic review. *Angle Orthodontist*, 80(5), 925-932.
2. Angelopoulou, M. V., Vlachou, V., and Halazonetis, D. J. (2012). Pharmacological management of pain during orthodontic treatment: a meta-analysis. *Orthodontics & Craniofacial Research*, 15(2), 71-83.
3. Jansen, J. P., Trikalinos, T., Cappelleri, J. C., Daw, J., Andes, S., Eldessouki, R., and Salanti, G. (2014). Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value in Health*, 17(2), 157-173.
4. Zhang, J., Carlin, B. P., Neaton, J. D., Soon, G. G., Nie, L., Kane, R., Virnig, B. A., and Chu, H. (2014). Network meta-analysis of randomized clinical trials: Reporting the proper summaries. *Clinical Trials*, 11(2), 246-262.
5. Sandhu, S. S., Cheema, M. S., and Khehra, H. S. (2016). Comparative effectiveness of pharmacologic and nonpharmacologic interventions for orthodontic pain relief at peak pain

- intensity: A Bayesian network meta-analysis. *American Journal of Orthodontics and Dentofacial Orthopedics*, 150(1), 13-32.
6. Piepho, H.-P. (2014). Network-meta analysis made easy: detection of inconsistency using factorial analysis-of-variance models. *BMC Medical Research Methodology*, 14(1), 61.
 7. Piepho, H. P., Williams, E. R., and Madden, L. V. (2012). The Use of Two-Way Linear Mixed Models in Multitreatment Meta-Analysis. *Biometrics*, 68(4), 1269-1277.
 8. Greco, T., Edefonti, V., Biondi-Zoccai, G., Decarli, A., Gasparini, M., Zangrillo, A., and Landoni, G. (2015). A multilevel approach to network meta-analysis within a frequentist framework. *Contemporary Clinical Trials*, 42, 51-59.
 9. Giovane, C. D., Vacchi, L., Mavridis, D., Filippini, G., and Salanti, G. (2013). Network meta-analysis models to account for variability in treatment definitions: application to dose effects. *Statistics in Medicine*, 32(1), 25-39.
 10. Sandhu, S. S., and Sandhu, J. (2013). A randomized clinical trial investigating pain associated with superelastic nickel–titanium and multistranded stainless steel archwires during the initial leveling and aligning phase of orthodontic treatment. *Journal of Orthodontics*, 40(4), 276-285.
 11. Bondemark, L., Fredriksson, K., and Ilros, S. (2004). Separation effect and perception of pain and discomfort from two types of orthodontic separators. *World Journal of Orthodontics*, 5(2), 172-176.
 12. Ngan, P., Kess, B., and Wilson, S. (1989). Perception of discomfort by patients undergoing orthodontic treatment. *American Journal of Orthodontics and Dentofacial Orthopedics*, 96(1), 47-53.
 13. Sandhu, S. S., Shetty, V. S., Mogra, S., Varghese, J., Sandhu, J., and Sandhu, J. S. (2012). Efficiency, behavior, and clinical properties of superelastic NiTi versus multistranded stainless steel wires: a prospective clinical trial. *Angle Orthodontist*, 82(5), 915-921.
 14. Higgins, J. P. T., and Green, S. (Eds.). (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*: The Cochrane Collaboration.
 15. Dias, S., Sutton, A. J., Welton, N. J., and Ades, A. E. (2013). Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Medical Decision Making*, 33(5), 618-640.
 16. Sandhu, S. S., and Sandhu, J. (2013). Orthodontic pain: an interaction between age and sex in early and middle adolescence. *Angle Orthodontist*, 83(6), 966-972.
 17. Sandhu, S. S., and Leckie, G. (2016). Orthodontic pain trajectories in adolescents: Exploring the between- and within-subject variability in pain perception. *American Journal of Orthodontics and Dentofacial Orthopedics*, 149(4), 491-500.
 18. Sandhu, S. S., and Sandhu, J. (2015). Effect of physical activity level on orthodontic pain perception and analgesic consumption in adolescents. *American Journal of Orthodontics and Dentofacial Orthopedics*, 148(4), 618-627.
 19. Sandhu, S. S., Sandhu, J., and Kaur, H. (2015). Reporting quality of randomized controlled trials in orthodontics—what affects it and did it improve over the last 10 years? *The European Journal of Orthodontics*, 37(4), 356-366.
 20. SAS Institute. (2013). *SAS/STAT® 13.1 User's Guide The GLIMMIX Procedure*: SAS Institute.
 21. StataCorp. (2015). *Stata: Release 14. Statistical Software*. College Station, TX: StataCorp LP.
 22. Chaimani, A., Higgins, J. P. T., Mavridis, D., Spyridonos, P., and Salanti, G. (2013). Graphical Tools for Network Meta-Analysis in STATA. *PloS One*, 8(10), e76654.
 23. Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods*, 3(2), 80-97.
 24. Bernhardt, M. K., Southard, K. A., Batterson, K. D., Logan, H. L., Baker, K. A., and Jakobsen, J. R. (2001). The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics*, 120(1), 20-27.

25. Bird, S. E., Williams, K., and Kula, K. (2007). Preoperative acetaminophen vs ibuprofen for control of pain after orthodontic separator placement. *American Journal of Orthodontics and Dentofacial Orthopedics*, 132(4), 504-510.
26. Bradley, R. L., Ellis, P. E., Thomas, P., Bellis, H., Ireland, A. J., and Sandy, J. R. (2007). A randomized clinical trial comparing the efficacy of ibuprofen and paracetamol in the control of orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics*, 132(4), 511-517.
27. Bruno, M. B., Bruno, M. A. D., Krymchantowski, A. V., da Motta, A. F. J., and Mucha, J. N. (2011). A double-blind, randomized clinical trial assessing the effects of a single dose of preemptive anti-inflammatory treatment in orthodontic pain. *Progress in Orthodontics*, 12(1), 2-7.
28. Gupta, M., Kandula, S., Laxmikanth, S. M., Vyavahare, S. S., Reddy, S. B., and Ramachandra, C. S. (2014). Controlling pain during orthodontic fixed appliance therapy with non-steroidal anti-inflammatory drugs (NSAID): a randomized, double-blinded, placebo-controlled study. *Journal of Orofacial Orthopedics*, 75(6), 471-476.
29. Kohli, S. S., and Kohli, V. S. (2011). Effectiveness of piroxicam and ibuprofen premedication on orthodontic patients' pain experiences. *Angle Orthodontist*, 81(6), 1097-1102.
30. Minor, V., Marris, C. K., McGorray, S. P., Yezierski, R., Fillingim, R., Logan, H., and Wheeler, T. T. (2009). Effects of preoperative ibuprofen on pain after separator placement. *American Journal of Orthodontics and Dentofacial Orthopedics*, 136(4), 510-517.
31. Ngan, P., Wilson, S., Shanfeld, J., and Amini, H. (1994). The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. *American Journal of Orthodontics and Dentofacial Orthopedics*, 106(1), 88-95.
32. Patel, S., McGorray, S. P., Yezierski, R., Fillingim, R., Logan, H., and Wheeler, T. T. (2011). Effects of analgesics on orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics*, 139(1), 53-58.
33. Polat, O., Karaman, A. I., and Durmus, E. (2005). Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain. *Angle Orthodontist*, 75(5), 791-796.
34. Polat, O., and Karaman, A. I. (2005). Pain control during fixed orthodontic appliance therapy. *Angle Orthodontist*, 75(2), 214-219.
35. Salmassian, R., Oesterle, L. J., Shellhart, W. C., and Newman, S. M. (2009). Comparison of the efficacy of ibuprofen and acetaminophen in controlling pain after orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics*, 135(4), 516-521.
36. Steen Law, S. L., Southard, K. A., Law, A. S., Logan, H. L., and Jakobsen, J. R. (2000). An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. *American Journal of Orthodontics and Dentofacial Orthopedics*, 118(6), 629-635.
37. Sudhakar, V., Vinodhini, T. S., Mohan, A. M., Srinivasan, B., and Rajkumar, B. K. (2014). The efficacy of different pre- and post-operative analgesics in the management of pain after orthodontic separator placement: A randomized clinical trial. *Journal of Pharmacy & Bioallied Sciences*, 6(Suppl 1), S80-84.
38. Zarif Najafi, H., Oshagh, M., Salehi, P., Babanouri, N., and Torkan, S. (2015). Comparison of the effects of preemptive acetaminophen, ibuprofen, and meloxicam on pain after separator placement: a randomized clinical trial. *Progress in Orthodontics*, 16, 34.
39. Mbizvo, G. K., Nolan, S. J., Nurmikko, T. J., and Goebel, A. (2015). Placebo responses in longstanding Complex Regional Pain Syndrome: a systematic review and meta-analysis. *Journal of Pain*, 16(2), 99-115.
40. Clarke, R., Derry, S., and Moore, R. A. (2012). Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev*(4), Cd004309.
41. Sinatra, R. S., Jahr, J. S., and Watkins-Pitchford, J. M. (2010). *The essence of analgesia and analgesics*: Cambridge University Press.

